Claims

1. Use of inhibitors of dipeptidyl peptidase IV (DP IV) as well as of inhibitors of enzymes having an equal substrate specificity (DP IV-analogous enzyme activity) or/and of inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as of inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity) for an inhibition of the proliferation (DNA synthesis) of human fibroblasts.

2. Use according to claim 1, wherein the DP IV inhibitors are Xaa-Pro-dipeptides (Xaa = α-amino acid or side chain-protected derivative), corresponding derivatives, more preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e. g. Pro-Boro-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-$(Xaa)_n$ peptides (Xaa = α-amino acid, n = 0 to 10), corresponding derivatives and their salts, amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa represents an α-amino acid or a side chain-protected derivative, preferably N^{ϵ}-4-nitrobenzyl-oxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines, for example pyrrolidine, piperidine, thiazolidine and their derivatives, represent the amide structure, and/or tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S, 2S', 2S")-2-[2'-[2"-amino-3"-(indole-3'"-yl-) 1"-oxoprolyl-]1', 2', 3', 4'-tetrahydro-6', 8'-dihydroxy-7-methoxy-isoquinol-3-yl-carbonylamino-] 4-hydroxymethyl-5-hydro-pentanoic acid (TMC-2A).

3. Use according to claim 1, wherein amino acid amides, preferably N^{ϵ}-4-nitrobenzyloxycarbonyl-L-lysine thiazolidide, pyrrolidide and piperidide as well as the corresponding 2-cyanothiazolidide, 2-cyanopyrrolidide and 2-cyanopiperidide derivative are used as the DP IV inhibitors.

4. Use according to claim 1, wherein the inhibitors of APN are actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β-amino thiols, α-amino phosphinic acids, α-amino phosphinic acid derivatives, preferably D-Phe-ψ-[PO(OH)-CH_2]-Phe-Phe and their salts.

5. Use of the inhibitor combinations according to any of the claims 1 to 4 for a prevention and therapy of benign fibrotic and sclerotic diseases (in particular post-infectious and post-traumatic: hypertrophic scars, keloids, dermatofibroms, fibrolipomes, disseminated (myo-) fibromatoses), as well as of malign fibroblast hyperproliferation states (for example fibrosarcomes, mixed tumors as atypical fibroxanthoma, malign fibrous histiocytoma, aggressive angiomyxoma, paraneoplasiae), of fibrotic autoimmune diseases as, for example, sclerodermia (circumscript sclerodermia, progressive-systemic sclerodermia, CREST syndrome), of dermatosclerosis accompanying other collagenoses and the graft-versus-host disease, of vitiligo (white spot disease, Lichen sclerosus et atrophicus), and of the heterogeneous group of pseudosclerodermiae (as, for example the eosinophilic/proliferative fascitis, pseudosclerodermiae generated by exogeneous causes as, for example, toxic oil syndrome, silicosis, porphyriae, eosinophilic myalgia syndrome, popular mucinosis (Lichen myxo-edematosus) or Borrelia-associated fibrosis states), of secondary sclerosis conditions as, for example, in the course of a stasis fibrosis accompanying chronic venous insufficiency or lipolymphedemas, in a fibrotic progressive stage of patternal alopecia (alopecia androgenetica) and of rare localized fibroblast diseases (Dupuytren's disease, Ledderhose's disease, "knuckle pads", penile induration (Peyronie's disease, induratio penis plastica).

6. Pharmaceutical preparations, comprising inhibitors of dipeptidyl peptidase IV (DP IV) as well as inhibitors of enzymes having DP IV-analogous

enzyme activity or/and inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as inhibitors of enzymes having APN-analogous enzyme activity, in combination with per se known carrier, additive and/or auxiliary substances.

7. Pharmaceutical preparations according to claim 6, comprising, as the DP IV inhibitors, Xaa-Pro-dipeptides (Xaa = α-amino acid or side chain-protected derivatives), corresponding derivatives, more preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e. g. Pro-Boro-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-$(Xaa)_n$ peptides (Xaa = α-amino acid, n = 0 to 10), corresponding derivatives and their salts, amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa represents an α-amino acid or a side chain-protected derivative, preferably N^{ϵ}-4-nitrobenzyloxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines, for example pyrrolidine, piperidine, thiazolidine and their derivatives, represent the amide structure.

8. Pharmaceutical preparations according to claim 6, comprising, as the DP IV inhibitors, preferably amino acid amides, for example N^{ϵ}-4-nitrobenzyloxycarbonyl-L-lysine thiazolidide, pyrrolidide and piperidide as well as the corresponding 2-cyanothiazolidide, 2-cyanopyrrolidide and 2-cyanopiperidide derivative.

9. Pharmaceutical preparations according to claim 6, comprising, as the APN inhibitors, actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β-amino thiols, α-amino phosphinic acids, α-amino phosphinic acid derivatives, preferably D-Phe-ψ-[PO(OH)-CH_2]-Phe-Phe and their salts.

10. Pharmaceutical preparations according to any of claims 6 to 9, comprising two or several inhibitors of DPIV or inhibitors of enzymes having a DPIV-analogous enzyme activity or/and inhibitors of APN or inhibitors having an APN-analogous enzyme activity in a spacely separated formulation in combination with per se known carrier, auxiliary and/or additive substances for a simultaneous or, with respect to time, immediately consecutive administration with the aim of a joint effect.

11. Pharmaceutical preparations according to any of claims 6 to 9 for a systemic application for an oral, transdermal, percutaneous, intravenous, subcutaneous, intracutaneous, intramuscular, rectal, vaginal, sublingual application together with per se known carrier, auxiliary and/or additive substances.

12. Pharmaceutical preparations according to any of claims 6 to 10 for a topical application in the form of creams, ointments, pastes, gels, solutions, sprays, liposomes or nanosomes, "pegylated" formulations, degradable depot matrices, mixable lotions, hydrocolloid dressings, plasters, microsponges, prepolymers or other dermatological bases/vehicles including instillative application.

13. A method for the therapy and prevention of dermatological diseases including a hyperproliferation and changed differentiation states of fibroblasts, comprising the administration of inhibitors of dipeptidyl peptidase IV (DPIV) as well as of inhibitors of enzymes having an equal substrate specificity (DPIV-analogous enzyme activity) or/and of inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as of inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity).

14. The method of claim 13, wherein one inhibitor or several inhibitors of the above enzymes or one or several preparation(s) containing those inhibitors singly or – preferably – in combination is/are administered to a patient, said inhibitors being selected from inhibitors of DPIV and particularly preferable from Xaa-Pro-dipeptides (Xaa = α-amino acid or side chain-protected derivative), corresponding derivatives, more preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e. g. Pro-Boro-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-$(Xaa)_n$ peptides (Xaa = α-amino acid, n = 0 to 10), corresponding derivatives and their salts, amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa represents an α-amino acid or a side chain-protected derivative, preferably N^{ϵ}-4-nitrobenzyloxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines, for example pyrrolidine, piperidine, thiazolidine and their derivatives, represent the amide structure, and/or tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S, 2S', 2S")-2-[2'-[2"-amino-3"-(indole-3'"-yl-) 1"-oxoprolyl-]1', 2', 3', 4'-tetrahydro-6', 8'-dihydroxy-7-methoxyisoquinol-3-yl-carbonylamino-] 4-hydroxymethyl-5-hydro-pentanoic acid (TMC-2A); and from inhibitors of APN and particularly preferable from actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β-amino thiols, α-amino phosphinic acids, α-amino phosphinic acid derivatives, preferably D-Phe-ψ-[PO(OH)-CH_2]-Phe-Phe and their salts.